

August 28, 2024

The Honorable Karen S. Marston
United States District Court for the
Eastern District of Pennsylvania
601 Market Street
Philadelphia, PA 19106

Re: *In re Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) Product Liability Litigation*, 2:24-md-03094: Defendants' Letter Brief On Frontloading General Causation Discovery

Dear Judge Marston:

INTRODUCTION

In response to the Court's request for additional briefing, Defendants respectfully submit this letter to address the Court's questions about the *Suboxone* MDL and regarding the Bradford Hill factors, including specifically how application of those factors may "influence the Court's consideration of whether general causation is in fact 'cross cutting' or instead, is more appropriately addressed on an individual Plaintiff by individual Plaintiff basis."¹ CMO #18 (Doc. No. 235) at 11, ¶ 15. For numerous reasons, this MDL is different from *Suboxone* and procedurally favors an approach that frontloads general causation discovery. Defendants look forward to the opportunity to further address these issues during Science Day on September 4, 2024.

First, the Court has recognized already that early resolution of preemption and warning adequacy "is likely to streamline the litigation," and the Court "direct[ed] the parties to meet and confer so that they are prepared to jointly propose deadlines for regulatory and company discovery" on those issues. *Id.* at 10, ¶ 14. Such discovery will substantially overlap with discovery related to general causation because the regulatory and company evidence relating to the appropriate contents of the labels (*e.g.*, clinical trial data, post-marketing pharmacovigilance, and regulatory communications) necessarily will also bear directly on the question of whether the medicines can cause the alleged injuries. Thus, in this MDL, accelerating general causation discovery would be particularly efficient given that the Court already has found it appropriate to do so with respect to the warnings and preemption issues. And Defendants will commit to working cooperatively with the Court and the Plaintiffs to ensure Plaintiffs' experts have the information necessary to address not just the warning and preemption issues, but also general causation.

Second, general causation—and Bradford Hill—focus on the threshold question of whether an exposure is capable of causing the alleged injury in anyone, regardless of any plaintiff-specific or case-specific factors. Accordingly, numerous MDL courts have recognized the efficiency advantages of bifurcating discovery and resolving threshold general causation issues

¹ See August 2, 2024, Status Conference Transcript, at 14:25-15:3 (seeking "additional briefing on how the Hill factors may affect the decision, the plaintiff's brief and the Suboxone opinion that I have looked at here and the other MDL denying bifurcation").

before engaging in bellwether discovery and workup. *See, e.g., In re Incretin Mimetics Prods. Liab. Litig.*, No. 13-md-2452, Doc. No. 325 (S.D. Cal.); *In re Viagra Prods. Liab. Litig.*, No. 06-md-1724, Doc. No. 38 (D. Minn.); *In re Acetaminophen - ASD-ADHD Prods. Liab. Litig.*, No. 22-md-3043, Doc. No. 246; *In re Onglyza (Saxagliptin) & Kombiglyze (Saxagliptin & Metformin) Prods. Liab. Litig.*, MDL No. 2809, Doc. No. 179 (E.D. Ky.); *In re Viagra (Sildenafil Citrate) Prods. Liab. Litig.*, MDL No. 2691, Doc. No. 102 (N.D. Cal.); *In re Baby Food, Prods. Liab. Litig.*, No. 3:24-md-03101, Doc. Nos. 128, 154 (N.D. Cal.). And, unlike in *Suboxone*, Defendants are not seeking to limit general causation discovery “to an artificially narrow body of knowledge that would likely interfere with the search for the truth of general causation or render any such determination unreliable or too attenuated from real-world science.” *In re Suboxone (Buprenorphine/Naloxone) Film Prods. Liab. Litig.*, 2024 WL 3157608, at *3 (N.D. Ohio June 24, 2024).

Third, in the event this MDL proceeds to a bellwether process, addressing general causation early will inform that process and help the Parties and the Court select cases in a manner that will aid in resolution of the overall litigation.

ARGUMENT

I. General Causation Discovery Can Occur in Parallel with, and on a Similar Timeline, as Preemption and Warnings Discovery.

This Court granted Defendants’ request for early discovery and motion practice as to preemption and warning adequacy, finding “a ruling on these issues is likely to streamline the litigation.” CMO #18 at 10, ¶ 14. This same early discovery ordered in CMO #18 will overlap extensively with discovery relevant to general causation. Accordingly, the *Suboxone* court’s concern regarding “costs in time and resources” associated with general causation discovery does not apply here. *See In re Suboxone*, 2024 WL 3157608, at *3. Indeed, efficiency in time and resources strongly favor frontloading general causation discovery here.

In the pharmaceutical context, federal preemption and warning adequacy issues are closely intertwined with scientific causation. Federal preemption analysis turns on two questions: (1) whether “newly acquired information” existed (information that was available to FDA) which provided “evidence of a causal association” such that the defendant manufacturer independently could have changed the FDA-approved product labeling; and/or (2) whether there is “clear evidence” that the FDA would have rejected the manufacturers’ efforts to do so. *See Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 300 (2019). Similarly, adequacy of warnings turns on whether the known risks of the medicine were reflected adequately in its FDA-approved product labeling, and frequently involves questions regarding when and which risks were known to the company. Accordingly, discovery related to preemption and adequacy of the warnings is likely to overlap significantly with discovery related to general causation.

Even if it were possible to separate discovery related to general causation, no good reason exists to do so. Discovery related to preemption and adequacy of warnings necessarily will include non-custodial documents (such as the full regulatory file—INDs, NDAs, clinical trial reports, adverse event data, preclinical data, and toxicology data) as well as relevant documents from key custodians in areas such as clinical, preclinical, regulatory, medical affairs, and

pharmacovigilance. These documents are likely to represent the bulk (if not the totality) of non-public information relevant to Plaintiffs' general causation claims. Accordingly, delaying consideration of general causation until a later time can only result in future redundant discovery requests, repeated depositions, and additional discovery disputes, ultimately slowing the proceedings and increasing the burden on the Court and the parties.

Furthermore, while the *Suboxone* court raised concerns about appropriately defining the scope of discovery relevant to general causation, noting that "information germane to general causation will likely go beyond INDs, NDAs, clinical trials and pharmacovigilance documents that Defendants seek to frontload" and might include "preclinical studies," "toxicology," and other information, those concerns do not apply here as Defendants do not seek to limit discovery in a manner similar to that proposed by the *Suboxone* defendants.² See *In re Suboxone*, 2024 WL 3157608, at *3. On the contrary, Defendants expect that already contemplated preemption discovery will include the vast majority of documents and information relevant to general causation, including custodial and regulatory files, and preclinical data and studies. While the specific custodians and search terms will need to be negotiated, and some disputes may arise, the Parties and the Court can work together to ensure that Plaintiffs and their experts have access to the information necessary to address both preemption and general causation.

Judge Anthony Battaglia—who at the time was overseeing the *Incretin* MDL, which involved claims that various other GLP-1 RAs cause pancreatic cancer—provided succinct instructions to the parties on the scope of general causation discovery, which he addressed in parallel with discovery related to preemption:

[P]ermitted discovery includes actual scientific evidence such as animal studies, clinical trials, epidemiologic data, adverse event reports, and submittal documents to scientific and government organizations including the FDA and EMA with regard to the causal link in dispute in this case. Any such documents, which would appear in the files in other departments of the Defendant organizations (i.e., marketing, sales, etc), would be discoverable, but general marketing, sales, licenses, consulting agreements, market share, third-party contracts, advertising, promotional, marketing, sales and/or public relations efforts or campaigns, as well as training documents for sales forces would not.

In re Incretin, No. 13-md-2452, Doc. No. 377, at 2. These instructions appropriately focused discovery on the scientific evidence that is at the core of general causation—regardless of its location—and are broadly consistent with approaches taken by other MDL courts that have frontloaded general causation discovery. See, e.g., *In re Acetaminophen*, Doc. No. 246; *In re Viagra*, No. 06-md-1724, Doc. No. 38; *In re Baby Food*, No. 24-md-03101, Doc. Nos. 128, 154;

² The *Suboxone* defendants suggested that discovery should focus on "actual scientific evidence such as clinical trial data, adverse event reports of dental adverse events, and submissions to scientific or governmental organizations relating to the question of whether Suboxone film can cause the dental injuries claimed in these cases," and noted that "internal company documents that are not within these categories are generally not relevant to the question of general causation." See *In re Suboxone*, 1:24-md-3029, Doc. No. 61, at 11-12.

In re Onglyza, MDL No. 2809, Doc. No. 179; *In re Viagra (Sildenafil Citrate)*, MDL No. 2691, Doc. No. 102. A similar approach would be appropriate here.

II. General Causation—and Bradford Hill—Are Independent of Plaintiff-Specific Facts.

General causation focuses on whether an exposure is capable of causing an injury in anyone, regardless of their medical or social history. It is fundamentally a population-based analysis that relies on epidemiologic evidence (*i.e.*, studies of diseases in populations such as clinical trials or observational studies). See *In re Zolofit (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 475 (E.D. Pa. 2014) (“When one is interested in human causation, the most relevant evidence will come from human epidemiological studies.”). It is independent of plaintiff-specific factors. As one court explained:

Causation has two levels, general and specific, and a plaintiff must prove both. General causation is whether a substance is capable of causing a particular injury or condition in the general population, while specific causation is whether a substance caused a particular individual's injury. Sequence matters: a plaintiff must establish general causation before moving to specific causation. Without the predicate proof of general causation, the tort claim fails.

In re Zolofit (Sertraline Hydrochloride) Prods. Liab. Litig., 176 F. Supp. 3d 483, 491 (E.D. Pa. 2016) (quoting *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 277-78 (5th Cir. 2010)), *aff'd*, 858 F.3d 787 (3d Cir. 2017).

The Bradford Hill criteria, which the *Suboxone* court discussed, are some of the most commonly used guidelines for evaluating general causation. A Bradford Hill analysis—like other general causation analyses—begins with a review of the available epidemiologic evidence to determine if an association exists at a population level. If no association exists, the inquiry ends. See *Reference Manual on Scientific Evidence* (3d ed. 2011) at 598-99 (“REF.MAN.”) (the Bradford Hill criteria “are employed only after a study finds an association to determine whether that association reflects a true causal relationship”); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 565 (E.D. Pa. 2003) (“Review of the criteria themselves, as set forth in the seminal remarks of Dr. Bradford-Hill, shows that an epidemiologic foundation is a prerequisite for application of his criteria.”); *In re Zolofit*, 26 F. Supp. 3d at 475 (“The Bradford-Hill criteria ask first whether there is evidence of a strong, well-replicated association between the variables of interest. . . .”). If, on the other hand, an association is found, researchers “look for alternative explanations for the association, such as bias or confounding factors.” REF.MAN. at 598. The focus of this inquiry is to determine whether the observed association is “valid,” or the result of some other, uncontrolled factor or error in the study.³ See, e.g., *In re Zolofit (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 464 (E.D. Pa. 2014) (discussing statistical artifacts, detection bias, and confounding by indication as potential alternative explanations for the observed association).

³ An example of this is an association reported in the early 1980s between coffee drinking and certain forms of cancer, which was later explained to be confounded by the propensity of coffee drinkers to smoke cigarettes.

If researchers determine that a valid association exists, they next “consider how guidelines for inferring causation from an association apply to the available evidence.” REF.MAN. at 598. In the context of Bradford Hill, experts typically consider nine factors: (1) temporal relationship, (2) strength of the association, (3) dose-response relationship, (4) replication of the findings, (5) biological plausibility (coherence with existing knowledge), (6) consideration of alternative explanations, (7) cessation of exposure, (8) specificity of the association, and (9) consistency with other knowledge.⁴ See *id.* at 599-600. It is important to emphasize that consideration of these factors is not dependent on either case- or plaintiff-specific factors.

For example, an expert evaluates the presence or absence of a dose-response relationship through analysis of data from clinical studies, assessing whether, in those studies, an adverse event of interest is more commonly observed at higher exposure levels. See *In re Acetaminophen*, 2023 WL 8711617, at *18 (S.D.N.Y. Dec. 18, 2023) (“A dose-response relationship exists where studies show that the greater the exposure, the greater the risk of disease.”). At this point, the dose an individual plaintiff took is not at issue. See REF.MAN. at 603, n.161 (“Evidence of a dose-response relationship as bearing on whether an inference of general causation is justified is analytically distinct from determining whether evidence of the dose to which a plaintiff was exposed is required in order to establish specific causation.”). The same is true for the other criteria discussed by the *Suboxone* court, all of which are evaluated based on review of scientific evidence, independent of any plaintiff-specific facts or information.⁵ Case-specific facts become relevant at the specific causation stage, after general causation has been established.

Accordingly, consideration and application of the Bradford Hill criteria in the context of general causation is “more appropriately addressed” early as a cross-cutting issue, rather than “on an individual Plaintiff by individual Plaintiff basis.” CMO #18 at 11, ¶ 15. Indeed, numerous MDL courts have expressly considered and applied the Bradford Hill criteria in the context of evaluating the reliability and admissibility of threshold general causation opinions without considering, and before conducting, case-specific discovery. See, e.g., *In re Acetaminophen*, 2023 WL 8711617, at *15 (excluding “experts [who] undertook Bradford Hill analyses” to conclude “that acetaminophen causes ASD and ADHD”); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 247 (S.D.N.Y. 2018) (excluding plaintiffs’ causation experts, including those who applied “Bradford Hill or on a similar totality-of-the-circumstances approach”), *aff’d*, 982 F.3d 113 (2d Cir. 2020); *In re Onglyza*, 93 F.4th 339, 347 (6th Cir. 2024) (affirming exclusion of causation expert who “inconsistently applied several Bradford Hill factors”); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prods. Liab. Litig.*, 424 F. Supp. 3d 781, 798-99 (N.D. Cal. 2020) (holding that the opinions of plaintiffs’ general causation experts

⁴ While no specific formula exists for applying these criteria, courts recognize that “the specific techniques by which the . . . Bradford Hill methodology is conducted must themselves be reliable according to the principles articulated in *Daubert*.” *In re Zolofit (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 796 (3d Cir. 2017).

⁵ Furthermore, biological plausibility alone is insufficient to establish causation. See *In re Zolofit*, 26 F. Supp. 3d at 475 (“Although the Court has found that the experts at issue have offered scientifically reliable opinions on biological plausibility, that is but one of the Bradford-Hill criteria.”); *Soldo*, 244 F. Supp. 2d at 569 (“Establishing the *plausibility* of a hypothesis is not the same as demonstrating that the hypothesis is correct.”).

“must be excluded” because “their weighing of the Bradford Hill factors d[id] not represent a faithful application of an accepted methodology”); *In re Nexium Eesomeprazole*, 662 F. App’x 528, 530 (9th Cir. 2016) (discussing Bradford Hill factors in affirming exclusion of plaintiffs’ general causation expert); *In re Zantac*, 644 F. Supp. 3d. 1075, 1233-38, 1254-55 (S.D. Fla. 2022) (excluding plaintiffs’ general causation experts who applied Bradford Hill criteria unreliably). The same approach is appropriate here.

III. Early Discovery Will Help the Court and the Parties Assess the Validity of Plaintiffs’ Causation Claims.

Finally, this MDL involves a wide range of alleged injuries and at least five different medicines, each of which have unique safety and efficacy profiles and, in some cases, different mechanisms of action. Whether Plaintiffs can provide admissible expert evidence for the alleged injuries and medicines is a critical threshold issue, which potentially can narrow the scope of the claims (both in terms of injuries and medicines) and will help inform the bellwether selection process (if one is needed). Indeed, it would be inefficient to select a certain bellwether case and conduct extensive case-specific discovery, only to determine on the eve of trial that evidence of general causation is lacking for that injury and/or that specific medicine. For these reasons, Defendants respectfully request that the Court frontload discovery related to general causation, in parallel with ongoing discovery related to preemption and adequacy of the warnings.

Respectfully submitted,

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cc: MDL Counsel of Record

CERTIFICATE OF SERVICE

I hereby certify that, on August 28, 2024, a true and correct copy of the foregoing Defendants' Letter Brief On Frontloading General Causation Discovery was electronically filed using the Court's CM/ECF system, causing notification of the filing to all counsel of record.

/s/ Loren H. Brown

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